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(54) Title: RADIOPAQUE POLYMERS AND METHODS FOR PREPARATION THEREOF

(57) Abstract

The invention is directed to a biomedical polymer having a number average molecular weight of at least 7.500, said polymer being substantially non-porous and having polymerized therein at least one monomer having at least one covalently bound iodine group.

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Title: Radiopaque polymers and methods for preparation thereof.

The present invention relates to a class of polymeric materials exhibiting radiopacity due to the fact that molecules containing covalently-bound iodine were built-in during polymerisation. Fields of application of such radiopaque polymers include, but are not limited to: medical materials (e.g. bone cements, catheters, and implants such as blood vessel prostheses and endovascular stents); veterinary materials (e.g. implants, catheters), and toys, especially small objects with the associated danger of being swallowed. Due to the presence of covalently bound iodine in the polymer post-operative assessment of the fate of implants, using X-ray scanning, is possible.

In the literature some experiments have been described, dealing with the polymerization of iodine containing monomers. These experiments did not result in any suitable materials, as the polymerization did not proceed to a sufficient high molecular weight, or the resulting material did possess hemolytic properties, which makes the material unsuitable for biomedical applications.

The present invention relates to a class of radiopaque biomedical polymeric materials having a number average molecular weight of at least 7500. These radiopaque materials are either: (i) polymers of a monomer molecule that contains covalently-bound iodine, or (ii) copolymers in which at least one of the different monomers contains covalently-bound iodine, or (iii) terpolymers or polymers of even higher complexity, in which at least one of the different monomers contains covalently-linked iodine.

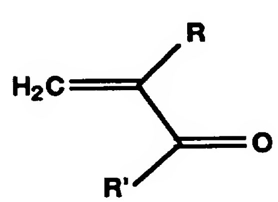
This group of polymers encompasses a wide variety of materials since a virtually unlimited variation is possible

for iodine containing monomers. Furthermore, the composition of copolymers, terpolymers, and other polymers such as mentioned under (ii) and (iii) can be varied, both in terms of relative concentration, and in terms of molecular structure of the different constituents.

Radiopaque polymers according to this invention are clearly distinguished with respect to prior art ("Preparation and evaluation of radiopaque hydrogel microspheres based on pHEMA/iothalamic acid and pHEMA/iopanoic acid as particulate emboli" A. Jayakrishnan et al., *Journal of Biomedical Materials Research*, **24**, 993-1004 (1990); "Synthesis and polymerization of some iodine-containing monomers for biomedical applications" A. Jayakrishnan et al., *Journal of Applied Polymer Science* **44**, 743-748 (1992)) in which it was reported that only low-molecular-weight products are obtained when acrylic derivatives of triiodophenol or iodothalamic acidare copolymerised with methyl methacrylate (MMA) or 2-hydroxyethyl methacrylate (HEMA).

The invention is explained in detail in the following: Although radiopaque polymers of different structural types are subject to this invention, the most predominant ones are polyacrylates and derivatives thereof. Preparation of radiopaque polyacrylates starts with synthesis of a monomer in which iodine is covalently bound. Molecules of this type include, but are not limited to the group of structures represented in Scheme I, which is divided into three subgroups (a, b, and c).

SCHEME I



subgroup a.: iodine in group R'.

R = H, CH_3, C_2H_5, or another organic substituent.

R' = I, O-C_6H_4I, O-$C_6H_3I_2$, O-$C_6H_2I_3$, NH-C_6H_4I, NH-$C_6H_3I_2$, NH-$C_6H_2I_3$, O-CH_2-CH_2-C(O)-C_6H_4I, O-CH_2-CH_2-O-C(O)-$C_6H_3I_2$, O-CH_2-CH_2-O-C(O)-$C_6H_2I_3$, NH-CH_2-CH_2-C(O)-C_6H_4I, NH-CH_2-CH_2-O-C(O)-$C_6H_3I_2$, NH-CH_2-CH_2-O-C(O)-$C_6H_2I_3$, or another organic iodine-containing substituent.

subgroup b.: iodine in group R:

R = I, CH_2I, CHI_2, CI_3, or another organic iodine-containing substituent.

R' = OCH_3, O-C_6H_5, O-CH_2-CH_2-OH, O-C_nH_{2n+1}, or other organic groups.

subgroup c.: other organic molecules containing at least one polymerizable double bond and one or more covalently linked iodine atoms are present in the structure.

The first method of preparation of monomers in subgroup a. of Scheme I starts our with an acylic acid chloride, e.g. methacryloyl chloride. These reactive compounds can be coupled to a variety of iodine-containing alcohols, in a reaction in which hydrogen chloride is formed along with the product. As an example, reaction of methacryloyl chloride with 4-iodophenol in the presence of a base (triethylamine) yields (4-iodophenyl) methacrylate. The latter compound clearly belongs to subgroup a in Scheme I. A variety of analogous monomers can be prepared according to this method. The only essential requirement is that one or more iodine atoms must be present in the alcohol. Use of an iodine containing amine instead of the alcohol will generate an amide bond. For example: reaction of methacryloyl chloride with 4-iodo-aniline in the presence of a strong base will lead to (4-iodophenyl) methacrylamide which also belongs to subgroup a. in Scheme I. Amides, derived from an acrylic acid chloride and an iodine-containing amine are explicitly included in subgroup a. of Scheme I.

The second method for generating compounds from subgroup a. in Scheme I starts our with an acrylate that is available, for instance from a commercial source. The acrylate is treated with an excess of an iodine-containing alcohol. Such a procedure leads to cleavage of the ester bond in the acrylate, and subsequently to substitution of the side-chain by the iodine containing group (trans-esterification). For example, methyl methacrylate can be treated with excess 4-iodophenol, and this reaction then affords 4-(iodophenyl) methacrylate. As said, the latter compound belongs to subgroup a. in Scheme I. The reaction can also be carried out with an iodine-containing amine, instead of the iodine-containing alcohol; an amide bond is generated in this case.

The third method for synthesising monomers of subgroup a. in Scheme I. is based on coupling of an acrylic compound with a free hydroxyl group or a free amino group, with an iodine-containing carboxylic acid. Two examples illustrate this approach. The first example relates to reaction of 2-hydroxyethyl methacrylate (HEMA) with 4-iodocarboxylic acid. This reaction, a normal esterification, can be carried out in many ways. It has been observed by the inventors that the reaction proceeds with excellent yield in the presence of N,N'-dicyclohexyl carbodiimide (DCC). Special care should be taken to isolate the product in pure form, i.e. to quantitatively remove the side product N,N'-dicyclohexyl urea. The second example relates to the analogous reaction of 2-aminoethyl methacrylate with 4-iodocarboxylic acid. This reaction also proceeds in the presence of DCC. Products obtained in reactions according to both examples belong to subgroup a. in Scheme I.

The fourth method of synthesis of monomers of subgroup a. in Scheme I is based on coupling of acrylate molecules with a free hydroxyl-, amino-, or other reactive nucleophilic group, with an iodine-containg acid chloride. In fact, this approach is the opposite of the first method of synthesis (vide supra). The procedure for executing the fourth method is therefore identical to the procedures for executing the first method.

Molecules belonging to subgroup b. in Scheme I. can be prepared according to prior art.

Molecules belonging to subgroup c. in Scheme I are iodine-containing congeners of molecules that are known to readily take part in copolymerisations with acrylates. For example, it is well known that styrene, N-vinyl-2-pyrollidone, or vinylacetate readily react with MMA, and/or HEMA in radical polymerisation reactions. Molecules in subgroup c. therefore include, but are not limited to, the structures in the attached Scheme II.

Polymer synthesis.

Two procedures for preparation of radiopaque acrylate polymers are disclosed. One method refers to synthesis in bulk, the other method refers to synthesis in solution. In the bulk procedure, an iodine-containing monomer (viz. Scheme I) is mixed with one or more other reactive monomers (e.g. MMA, HEMA, styrene), an initiator (e.g. molecules with the property of undergoing homolytic bond cleavage upon raising the temperature, e.g. acyl peroxides, cumyl- or tert. butyl peroxides, tetrazenes, AIBN, also: reagents that can be used in photopolymerisations, redoxinitiation), and a chain-transfer agent (e.g. mercapto ethanol). The reaction mixture is transferred into a Teflon tube which is tightly closed with a glass stopper on one end. The tube is then subjected to a controlled heat treatment. This affords the radiopaque materials as transparent glassy rods.

In the solution procedure, an iodine-containing monomer (viz. Scheme I) is mixed with one or more other reactive monomers (e.g. MMA, HEMA, styrene), an initiator (vide supra), and a chain-transfer agent (e.g. mercapto ethanol). This mixture is dissolved in a clean, high-boiling solvent (e.g. dimethylformamide, dimethyl-sulfoxide). The resulting solution is stirred continuously and subjected to a controlled heat treatment. After work-up, this renders a radiopaque polymer as

a white solid. Work-up can be cumbersome, since removal of the last traces of high-boiling solvent is often difficult. Pure product can be obtained after repeated washing steps, and lyophilisation.

With respect to the polymers that were obtained according to both procedures, it was found that a content of ca. 20 mol% of iodine-containing monomer ensures sufficient visibility using clinically common imaging techniques based on X-ray absorption. Thin fibers of materials as described above (content of iodine-containing monomer ca. 20 mol %) were clearly visible under routine fluoroscopy, even when a correction was applied for X-absorption due to the human body (a 15-cm thick layer of PMMA glass was placed in the X-ray beam). It must be noted that the content of 20 mol % refers to monomers with one iodine per molecule. Evidently, use of a monomer with two (three) iodine atoms per molecule will lead to clear visibility at a content of only 10 (7) mol %.

The polymers of the present invention can, as has been indicated above, be used for various biomedical purposes, which means that they have to be compatible in the human or animal body. More in particular suitable biomedical materials do not possess hemolytic properties. More in partiular the materials according to the invention are suitable as bone cements, catheters, and implants such as blood vessel prostheses and endovascular stents (in general medical materials); veterinary materials (e.g. implants, catheters), and toys, especially small objects with the associated danger of being swallowed.

The invention also relates to a monomer mixture that is suitable for preparing a biomedical polymer containing covalently bound iodine, said monomer mixture comprising at least one monomer having at least one iodine group covalently bound thereto, at least one reaction initiator and/or catalyst, optionally one or more other monomers not containing iodine and fillers. Preferably said monomer mixture is provided in the form of a two-pack system that is suitable for

in-situ use, for example as bone cement, as dental filling material, or as biomedical construction material.

The invention is elucidated on the basis of the following examples that are not intended to restrict the invention.

Examples

Example 1

Polymers A, B and C were prepared using the bulk polymerization method. The composition of the polymers is as follows:

Polymer A: 80 mol % MMA, 20 mol % [4-iodophenyl]methacrylate;

Polymer B: 65 mol % MMA, 15 mol % HEMA, 20 mol % [4-iodophenyl]methacrylate;

Polymer C: 60 mol % MMA, 19 mol % HEMA, 21 mol % 2-[4-iodobenzoyl]ethyl methacrylate.

Some physico-chemical data on these polymers are summarized in Table I.

Table I. Physico-chemical properties of some iodine-containing radiopaque polymers.

Pol[1]	Mw[2]	Mn[2]	Xray -visibility[3]	contact angle[4]	purity check[5]	monomer content
A	61.5	22.7	++	52.4	NMR, GPC	< 1 %
B	41.3	12.2	++	43.1	NMR, GPC	< 1 %
C	43.1	7.9	++	42.8	NMR, GPC	< 1 %

[1]Polymer A: 80 mol % MMA, 20 mol % [4-iodophenyl]methacrylate;
Polymer B: 65 mol % MMA, 15 mol % HEMA, 20 mol % [4-iodophenyl]methacrylate;
Polymer C: 60 mol % MMA, 19 mol % HEMA, 21 mol % 2-[4-iodobenzoyl]ethyl methacrylate.

[2]Determined by gel permeation chromatography, using polystyrene standards; expressed in kg/mol.

[3]Visibility under routine fluoroscopy, absorption of X-rays due to surrounding bone and tissue mimicked by 15 cm of Plexi

glass.
4 Measured according to the dynamic Wilhelmy plate technique; listed data are receding contact angles, expressed in degrees.
5Proton NMR measurements at 400 MHz, measured on solutions of polymers A-C in DMSO solution.

Some biochemical data on these polymers are summarized in Table II.

Table II. Biochemical properties of some iodine-containing radiopaque polymers.

Polymer[1]	**Clotting time**[2]	**platelet adhesion**[3]	**platelet morphology**[3]
A	392	10 %	unchanged
B	553	no	-------
C	700	10 %	spreaded

[1]See legend Table 1.
[2]Measured in a routine thrombin generation test procedure, expressed in seconds.
[3]Determined by scanning electron microscopy.
Polymers B and C were designed such that they combine X-ray visibility with enhanced biocompatibility. This is a unique feature.

Example 2

A copolymer, composed of methylmethacrylate (MMA, 51 mole %), and 2-[2'-iodobenzoyl] ethylmethacrylate (49 mole %), was prepared in a typical bulk synthesis (vide supra). The material showed Mw = 80.000 and Mn = 36000 (GCP analysis) while the residual monomer content was substantially smaller than 1%. The material was first granulated and subsequently powdered. The powder was then thoroughly mixed with polymethylmethacrylate (pMMA) powder, in the ratio 1:8 (w/w). A peroxide was added in the ratio 1:200 (w/w). The resulting powder was used to replace the solid component of a commercial

bone cement kit. The commercial liquid bone cement component was mixed with the powder. This yielded a cement, which hardened in 10-20 minutes. Mechanical tests of the material revealed that the tensile strength of the cement containing the radiopaque copolymer is 58 MPa, which is substantially larger than that for the commercial bone cement (48 MPa). The commercial bone cement was made radiopaque through addition of 10% (by weight) of barium sulfate. Apparently, the addition of barium sulfate (which does not mix with the polymeric cement matrix, and tends to form clumps) in fact weakens the cement. This problem can be solved via the use of a radiopaque (copolymer) as described in this example. Moreover, leaching a toxic barium sulfate cannot occur with the proposed new cement.

CLAIMS

1. Biomedical polymer having a number average molecular weight of at least 7.500, said polymer being substantially non-porous and having polymerized therein at least one monomer having at least one covalently bound iodine group.

2. Polymer according to claim 1, wherein at least 20% of the number of polymerized monomers contains said covalently bound iodine.

3. Polymer according to claim 1 or 2, wherein said monomer having iodine covalently bound is a reactive monomer having a iodine containing group attached thereto after polymerization.

4. Monomer mixture suitable for preparing a polymer according to claim 1-3, comprising at least one monomer having at least one iodine group covalently bound thereto, at least one reaction initiator and/or catalyst, optionally one or more other monomers not containing iodine and fillers.

5. Use of the monomer mixture according to claim 4 as a bone cement, as a dental filling material or as a bio-medical construction material.

INTERNATIONAL SEARCH REPORT

Inte mal Application No
PCI/NL 95/00277

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L29/00 A61L27/00 A61L25/00 A61L31/00 A61K6/083
C08F220/12 C08F214/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L A61K C08F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF APPLIED POLYMER SCIENCE, vol. 44, 1992 NEW YORK US, pages 743-748, JAYAKRISHNAN A. 'SYNTHESIS AND POLYMERIZATION OF SOME IODINE-CONTAINING MONOMERS FOR BIOMEDICAL APPLICATIONS' cited in the application see page 745, line 41 see page 746, line 31 - line 37 ---	1,2,4,5
X	GB,A,609 156 (WINGFOOT) 27 September 1948 see page 1, line 66 see page 2, line 24 - line 38; claims 1,5,6 ---	4
X	WO,A,82 01006 (NATIONAL RESEARCH DEVELOPMENT) 1 April 1982 see page 2, line 11 ---	1-5

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
23 November 1995	01. 12. 95

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,1 060 365 (HOECHST) 1 March 1967 see page 1, line 75; claim 1 ---	1,4
A	EP,A,0 452 123 (BECTON DICKINSON) 16 October 1991 see abstract ---	1
A	WO,A,87 07155 (CRITIKON) 3 December 1987 see page 11, line 3 ---	1
A	EP,A,0 523 928 (CRITIKON) 20 January 1993 see page 4, line 56 -----	1

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INTERNATIONAL SEARCH REPORT

..iformation on patent family members

Inte nal Application No
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